ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2003, p. 1681–1688 Vol. 47, No. 5
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.5.1681–1688.2003

Surveillance for Antimicrobial Susceptibility among Clinical Isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from Hospitalized Patients in the United States, 1998 to 2001

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Received 22 October 2002/Returned for modification 21 January 2003/Accepted 14 February 2003

***Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the most prevalent nonfermentative bacterial species isolated from clinical specimens of hospitalized patients. A surveillance study of 65 laboratories in the United States from 1998 to 2001 found >90% of isolates of *P. aeruginosa* from hospitalized patients to be susceptible to amikacin and piperacillin-tazobactam; 80 to 90% of isolates to be susceptible to cefepime, ceftazidime, imipenem, and meropenem; and 70 to 80% of isolates to be susceptible to ciprofloxacin, gentamicin, levofloxacin, and ticarcillin-clavulanate. From 1998 to 2001, decreases in antimicrobial susceptibility (percents) among non-intensive-care-unit (non-ICU) inpatients and ICU patients, respectively, were greatest for ciprofloxacin (6.1 and 6.5), levofloxacin (6.6 and 3.5), and ceftazidime (4.8 and 3.3). Combined 1998 to 2001 results for *A. baumannii* isolated from non-ICU inpatients and ICU patients, respectively, demonstrated that >90% of isolates tested were susceptible to imipenem (96.5 and 96.6%) and meropenem (91.6 and 91.7%); fewer isolates from both non-ICU inpatients and ICU patients were susceptible to amikacin and ticarcillin-clavulanate (70 to 80% susceptible); and <60% of isolates were susceptible to ceftazidime, ciprofloxacin, gentamicin, or levofloxacin. From 1998 to 2001, rates of multidrug resistance (resistance to at least three of the drugs ceftazidime, ciprofloxacin, gentamicin, and imipenem) showed small increases among *P. aeruginosa* strains isolated from non-ICU inpatients (5.5 to 7.0%) and ICU patients (7.4 to 9.1%). From 1998 to 2001, rates of multidrug resistance among *A. baumannii* strains isolated from non-ICU inpatients (27.6 to 32.5%) and ICU patients (11.6 to 24.2%) were higher and more variable than those observed for *P. aeruginosa*. Isolates concurrently susceptible, intermediate, or resistant to both imipenem and meropenem accounted for 89.8 and 91.2% of *P. aeruginosa* and *A. baumannii* isolates, respectively, studied from 1998 to 2001. In conclusion, for aminoglycosides and most β-lactams susceptibility rates for *P. aeruginosa* and *A. baumannii* were constant or decreased only marginally (≤3%) from 1998 to 2001. Greater decreases in susceptibility rates were, however, observed for fluoroquinolones and ceftazidime among *P. aeruginosa* isolates.**

Pseudomonas aeruginosa and *Acinetobacter baumannii* are nonfermentative gram-negative bacteria that have minimal nutritional requirements and can survive on a wide variety of surfaces and in aqueous environments. *P. aeruginosa* and *A. baumannii* rarely cause serious infections in otherwise healthy persons and are infrequently identified as normal microbial flora in healthy individuals (18, 30). Infections with *P. aeruginosa* or *A. baumannii* are of greatest concern for hospitalized patients, particularly those in intensive-care units (ICUs), where these opportunistic pathogens are capable of causing severe invasive infections in critically ill and immunocompromised patients. Patients with cystic fibrosis, neutropenia, iatrogenic immunosuppression, or disrupted anatomical barriers that normally prevent bacterial invasion (e.g., skin) are at risk of infection with *P. aeruginosa* or *A. baumannii* (9, 18, 30). Rates of colonization with *P. aeruginosa* and *A. baumannii* increase in hospitalized patients, particularly in those who have been hospitalized for extended periods of time and/or have received broad-spectrum antimicrobial therapy or cancer chemotherapy (18, 30). The spectrum of human infections caused by *P. aeruginosa* ranges from superficial skin infections to fulminant sepsis. *P. aeruginosa* is the leading cause of nosocomial respiratory infections and is of particular concern for intubated persons and patients with ventilator-associated pneumonia (18, 27). Hospital-acquired infections with *A. baumannii* also most commonly involve the respiratory tract; like *P. aeruginosa*, *A. baumannii* also causes nosocomial urinary tract infections and wound infections, and infections may progress to septicemia (30). *P. aeruginosa* has been documented previously to be responsible for morbidity and mortality in AIDS patients with advanced disease and, as a result of recent improvements in patient management, to be less commonly involved in febrile neutropenia and burn wound sepsis than previously observed (27).

P. aeruginosa and *A. baumannii* are resistant to antimicrobials from several different structural classes, either intrinsically or through acquisition of genetic determinants for resistance over time. Most isolates of *P. aeruginosa* and *A. baumannii* are resistant to ampicillin, amoxicillin-clavulanate, antistaphylococcal penicillins, narrow- and extended-spectrum cephalospo-

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rins (except ceftazidime and cefepime), tetracyclines, macrolides, rifampin, and chloramphenicol. *P. aeruginosa* is also resistant to ampicillin-sulbactam and trimethoprim-sulfamethoxazole, while many clinical isolates of *A. baumannii* are resistant to gentamicin and fluoroquinolones. In *P. aeruginosa* and *A. baumannii* antimicrobial resistance may arise because of outer membrane impermeability, increased activity of multidrug efflux pumps, target site alterations, or enzymatic degradation (e.g., aminoglycoside-modifying enzymes and β-lactamases). Resistance to noncarbapenem β-lactams in *P. aeruginosa* (18, 27) and *A. baumannii* (30) is most commonly associated with overproduction of a naturally produced cephalosporinase (AmpC). Antimicrobial resistance among clinical isolates of *P. aeruginosa* and *A. baumannii* may complicate the treatment of infections and can adversely affect clinical outcomes and patient treatment costs (6, 13). New antimicrobial agents with activity against *P. aeruginosa* and *A. baumannii* will not be available in the near future, making ongoing surveillance of the activities of currently available agents very important. The present study investigated the in vitro activities of 10 commonly tested antimicrobial agents against *P. aeruginosa* and *A. baumannii* isolated from non-ICU inpatients and ICU patients in U.S. hospitals from 1998 to 2001.

MATERIALS AND METHODS

Antimicrobial susceptibility testing results. The Surveillance Network (TSN) Database-USA (Focus Technologies, Herndon, Va.) was used as the source of antimicrobial susceptibility testing results for this study. TSN electronically assimilates antimicrobial susceptibility testing and patient demographic data from a network of hospitals in the United States (29). Laboratories are included in TSN based on factors such as hospital bed size, patient population, geographic location, and antimicrobial susceptibility testing methods used (29). Susceptibility testing of patient isolates is conducted onsite by each participating laboratory as a part of their routine diagnostic testing. Only data generated by Food and Drug Administration-approved testing methods with MIC results interpreted according to NCCLS recommendations (22) are included in TSN.

The antimicrobial susceptibility testing results included in the present analysis were restricted to the 65 U.S. laboratories that participated in TSN from 1998 to 2001 and that reported results for >50 isolates of *P. aeruginosa* per year, each isolate originating from a different hospital inpatient. The 65 laboratories were distributed across all nine U.S. Bureau of the Census regions. Isolates of *A. baumannii* were limited to those from the 24 U.S. laboratories that participated in TSN from 1998 to 2001 and that reported results for >20 isolates per year from different hospital inpatients. The 24 laboratories were distributed across six of the nine U.S. Bureau of the Census regions. Isolate results from all specimen sources were used. If the same patient had multiple isolates tested in a year, results from the first isolate in a year were used. For some analyses, data from ICU patients were analyzed separately from those of non-ICU hospital inpatients; data from patients in nursing facilities and hospital outpatients were excluded from the analysis. The prevalence of multidrug resistance (MDR) was investigated among isolates of *P. aeruginosa* and *A. baumannii* tested with ceftazidime, ciprofloxacin, gentamicin, and imipenem. Isolates resistant to three or all four antimicrobials were considered multidrug resistant (MDR).

RESULTS

Results for one or more antimicrobial agents were available for 76,211 isolates of *P. aeruginosa* and 7,394 isolates of *A. baumannii* from non-ICU inpatients and ICU patients from 1998 to 2001. Combined 1998 to 2001 results for *P. aeruginosa* demonstrated that >90% of isolates tested were susceptible to amikacin and piperacillin-tazobactam; from 80 to 90% of isolates were susceptible to cefepime, ceftazidime, imipenem, and meropenem; and from 70 to 80% of isolates were susceptible to ciprofloxacin, gentamicin, levofloxacin, and ticarcillin-clavulanate (Table 1). Rates of susceptibility to amikacin, cefepime, gentamicin, imipenem, meropenem, piperacillin-tazobactam, and ticarcillin-clavulanate differed by ≤3% from 1998 to 2001 for isolates from non-ICU inpatients and from ICU patients. Rates of susceptibility to ceftazidime from 1998 to 2001 decreased by 4.8 and 3.3% for isolates from non-ICU inpatients and ICU patients, respectively. Greater chronological decreases in susceptibility were observed for isolates from non-ICU inpatients and ICU patients, respectively, tested with ciprofloxacin (6.1 and 6.5%) and levofloxacin (6.6 and 3.5%). Based on cumulative 1998 to 2001 results, differences in susceptibility between isolates from non-ICU inpatients and those from ICU patients were ≤3% for amikacin, gentamicin, cefepime, ciprofloxacin, levofloxacin, and piperacillin-tazobactam. Susceptibility was higher among isolates from non-ICU inpatients than among isolates from ICU patients for ceftazidime (3.6%), ticarcillin-clavulanate (4.4%), imipenem (6.4%), and meropenem (7.3%).

Table 2 summarizes the contribution of ceftazidime, ciprofloxacin, gentamicin, and imipenem (antimicrobial class representatives) resistance to MDR phenotypes (defined in Materials and Methods) for clinical isolates of *P. aeruginosa* from 2001 tested with at least those four agents. By our definition of MDR, 7.0% (625 of 8,874) of isolates from non-ICU inpatients and 9.1% (206 of 2,271) of isolates from ICU patients were MDR in 2001. In 1998, 1999, and 2000, 5.5% (682 of 12,364), 6.4% (696 of 10,951), and 6.3% (641 of 10,170) of isolates from non-ICU inpatients were MDR, respectively; among isolates from ICU patients, 7.4% (174 of 2,362), 7.0% (155 of 2,202), and 9.5% (202 of 2,128) were MDR. The most common agent involved in MDR was ciprofloxacin (94.7 to 97.1% of all MDR isolates) from 1998 to 2001. All agents were a component of MDR more often among ICU patient isolates than among non-ICU inpatient isolates, except for ceftazidime. Analysis of ciprofloxacin-resistant isolates of *P. aeruginosa* ($n = 449$) from 2001 found that they were usually resistant to levofloxacin (86.9%) and also commonly resistant to ticarcillin-clavulanate (58.4%). When isolates from 2001 that were tested with all 10 agents were analyzed by carbapenem susceptibility status, all agents other than ceftazidime (for ICU patients) demonstrated ≥4%-higher resistance rates among meropenem-resistant isolates than among imipenem-resistant isolates for both non-ICU inpatients and ICU patients (Table 3). The greatest observed difference was a 27.4%-higher rate of resistance to ticarcillin-clavulanate among meropenem-resistant isolates than among imipenem-resistant isolates from non-ICU inpatients.

Table 4 compares NCCLS-defined (22) imipenem and meropenem susceptibility, intermediate, and resistance phenotypes for combined non-ICU inpatient and ICU patient isolates by year from 1998 to 2001. Interpretative phenotype agreement for imipenem and meropenem (i.e., imipenem-susceptible–meropenem-susceptible, imipenem-intermediate–meropenem-intermediate, and imipenem-resistant–meropenem-resistant) was 89.8% for combined 1998 to 2001 isolates and had a narrow range (88.7 to 91.6%) per annum over the 4 years studied (data not shown). The most common discordant phenotypes observed were imipenem-resistant–meropenem-susceptible (3.1% of isolates) and imipenem-resistant–meropenem-intermediate

TABLE 1. Per-annum and combined 1998 to 2001 in vitro susceptibilities to 10 antimicrobial agents for clinical isolates of *P. aeruginosa* from non-ICU inpatients and ICU patients in the United States

Antimicrobial	Yr	No. of isolates		% Susceptible		% Intermediate		% Resistant	
		Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU
Amikacin	1998	12,689	2,456	91.6	93.9	4.1	3.4	4.3	2.7
	1999	11,675	2,306	92.7	93.5	2.5	2.9	4.8	3.6
	2000	10,174	2,052	92.6	92.4	2.8	3.4	4.6	4.1
	2001	9,648	2,331	91.1	92.5	3.6	3.0	5.3	4.5
	1998–2001	44,186	9,145	92.0	93.1	3.3	3.2	4.7	3.7
Cefepime	1998	5,910	1,116	82.0	80.2	9.2	10.2	8.7	9.6
	1999	7,470	1,581	82.2	80.0	10.2	12.7	7.5	7.3
	2000	7,811	1,532	82.9	81.7	9.7	10.6	7.4	7.7
	2001	8,385	2,228	81.5	81.2	10.3	11.4	8.2	7.4
	1998–2001	29,576	6,457	82.2	80.8	9.9	11.3	7.9	7.8
Ceftazidime	1998	15,831	3,139	88.8	85.2	4.4	5.6	6.8	9.2
	1999	14,478	2,859	87.5	84.4	4.8	5.9	7.7	9.7
	2000	13,487	2,798	85.6	80.9	6.1	7.8	8.3	11.3
	2001	12,350	3,391	84.0	81.9	6.6	8.5	9.4	9.7
	1998–2001	56,146	12,187	86.6	83.1	5.4	7.0	8.0	9.9
Ciprofloxacin	1998	16,056	3,102	75.9	78.5	3.8	3.2	20.3	18.3
	1999	14,695	2,932	73.7	77.3	4.0	2.6	22.3	20.1
	2000	12,946	2,790	72.2	74.8	3.4	2.3	24.4	22.9
	2001	11,024	2,987	69.8	71.9	4.0	3.0	26.2	25.0
	1998–2001	54,721	11,811	73.2	75.7	3.8	2.8	23.0	21.5
Gentamicin	1998	16,901	3,311	79.5	78.5	6.3	6.8	14.2	14.8
	1999	15,861	3,265	78.2	78.0	7.0	6.3	14.8	15.7
	2000	14,837	3,088	78.2	76.1	7.0	5.8	14.8	18.1
	2001	13,311	3,718	76.6	75.9	8.2	8.0	15.2	16.2
	1998–2001	60,910	13,382	78.2	77.1	7.1	6.8	14.7	16.1
Imipenem	1998	13,189	2,600	87.2	78.9	2.4	3.4	10.4	17.7
	1999	12,056	2,568	86.6	81.3	2.5	2.8	10.9	15.9
	2000	11,197	2,427	86.9	80.2	2.0	2.8	11.1	17.0
	2001	9,762	2,538	85.5	80.7	2.7	3.0	11.8	16.3
	1998–2001	46,204	10,133	86.6	80.3	2.4	3.0	11.0	16.7
Levofloxacin	1998	4,776	339	75.3	75.2	4.7	4.4	20.0	20.4
	1999	8,542	959	73.5	70.1	4.3	4.6	22.2	25.3
	2000	10,698	1,652	70.5	74.5	3.8	3.0	25.7	22.5
	2001	9,345	2,146	68.7	71.7	4.1	3.8	27.2	24.5
	1998–2001	33,361	5,096	71.4	72.5	4.2	3.7	24.4	23.7
Meropenem	1998	719	95	85.7	77.9	2.5	4.2	11.8	17.9
	1999	1,009	46	85.1	73.9	3.2	8.7	11.7	17.4
	2000	2,088	292	86.9	77.1	3.9	7.5	9.2	15.4
	2001	2,157	543	85.5	80.1	3.8	4.4	10.7	15.5
	1998–2001	5,973	976	86.0	78.7	3.6	5.5	10.5	15.8
Piperacillin-tazobactam	1998	4,821	1,229	92.7	89.7	—[a]	—	7.3	10.3
	1999	7,663	1,638	91.8	91.9	—	—	8.2	8.1
	2000	10,140	2,041	92.8	90.8	—	—	7.2	9.2
	2001	9,963	2,986	91.6	91.8	—	—	8.4	8.2
	1998–2001	32,587	7,894	92.2	91.2	—	—	7.8	8.8
Ticarcillin-clavulanate	1998	7,355	1,773	79.8	73.9	—	—	20.2	26.1
	1999	5,627	1,347	77.3	75.6	—	—	22.7	24.4
	2000	4,610	1,099	77.9	73.6	—	—	22.1	26.4
	2001	3,548	961	76.9	71.5	—	—	23.1	28.5
	1998–2001	21,140	5,180	78.3	73.8	—	—	21.7	26.2

[a] —, NCCLS breakpoint unavailable.

(2.3% of isolates); however, all possible interpretative phenotype combinations were observed in each year. Major error (i.e., susceptible to one carbapenem and resistant to the other) and minor error (i.e., intermediate to one carbapenem and susceptible or resistant to the other) rates were 4.3 (per-annum variation, 2.4 to 5.2%) and 5.8% (per-annum variation, 4.4 to 6.1%) for 1998 to 2001 (data not shown).

P. aeruginosa data analysis stratifying antimicrobial suscep-

TABLE 2. Contribution of resistance to individual antimicrobials to MDR phenotypes among clinical isolates of *P. aeruginosa* in 2001

Patient group	No. of agents to which isolates were resistant	Total % of isolates (no.)	% of isolates (no.) resistant to:			
			Ceftazidime	Ciprofloxacin	Gentamicin	Imipenem
Non-ICU inpatients[a]	0	64.3 (5,708)	0 (0)	0 (0)	0 (0)	0 (0)
	1	18.5 (1,644)	12.2 (200)	58.6 (964)	11.3 (186)	17.9 (294)
	2	10.1 (897)	20.2 (181)	85.1 (763)	32.2 (289)	62.5 (561)
	3	5.4 (481)	55.3 (266)	93.1 (448)	69.4 (334)	82.1 (395)
	4	1.6 (144)	100 (144)	100 (144)	100 (144)	100 (144)
ICU patients[b]	0	61.8 (1,403)	0 (0)	0 (0)	0 (0)	0 (0)
	1	18.4 (417)	14.4 (60)	46.8 (195)	21.1 (88)	17.7 (74)
	2	10.8 (245)	22.4 (55)	80.4 (197)	36.3 (89)	60.8 (149)
	3	6.7 (153)	32.0 (49)	96.1 (147)	85.6 (131)	86.3 (132)
	4	2.3 (53)	100 (53)	100 (53)	100 (53)	100 (53)

[a] 7.0% (625 of 8,874) of isolates were resistant to three or more antimicrobials and defined as MDR. The most frequent MDR phenotype was concurrent resistance to ciprofloxacin, imipenem, and gentamicin, and this accounted for 34.4% of MDR isolates in 2001. Percentages of isolates that were MDR in 1998, 1999, and 2000 were 5.5, 6.4, and 6.3, respectively.

[b] 9.1% (206 of 2,271) of isolates were resistant to three or more antimicrobials and defined as MDR. The most frequent MDR phenotype was concurrent resistance to ciprofloxacin, imipenem, and gentamicin, and this accounted for 50.5% of MDR isolates. Percentages of isolates that were MDR in 1998, 1999, and 2000 were 7.4, 7.0, and 9.5, respectively.

tibility data by patient age group produced two notable observations (Table 5). Susceptibility to each agent was highest among patients ≤10 years of age. The difference in susceptibility between patients ≤10 years of age and those >60 years was greatest for levofloxacin (26.7%) and ciprofloxacin (24.1%); differences for all other agents were <10%.

Cumulative 1998 to 2001 results for *A. baumannii* isolated from non-ICU and ICU patients, respectively, demonstrated that >90% of isolates tested were susceptible to imipenem (96.5 and 96.6%) and meropenem (91.6 and 91.7%); fewer isolates (70 to 80%) were susceptible to amikacin and ticarcillin-clavulanate, and <60% of isolates were susceptible to ceftazidime, ciprofloxacin, gentamicin, and levofloxacin (Table 6). Susceptibility rates among non-ICU inpatients differed by ≤5% from 1998 to 2001 for all agents except ciprofloxacin, meropenem, and piperacillin-tazobactam; among ICU patient isolates susceptibility rates differed by ≤5% for imipenem, levofloxacin, and meropenem (data not shown). In 2001, the rates of MDR among *A. baumannii* strains tested with ceftazidime, ciprofloxacin, gentamicin, and imipenem were 32.5% (226 of 695) for isolates from non-ICU inpatients and 24.2% (70 of 289) for isolates from ICU patients. In 1998, 1999, and 2000, 27.6% (362 of 1,312), 20.1% (165 of 819), and 22.9% (186 of 812) of isolates from non-ICU inpatients were MDR, respectively; among isolates from ICU patients, 11.6% (37 of 320), 15.4% (39 of 254), and 26.5% (81 of 306) were MDR. Greater than 96.6% of all MDR isolates from 1998 to 2001 were resistant to ceftazidime, ciprofloxacin, and gentamicin while only 10.2% of MDR isolates were resistant to imipenem. In contrast to the data for *P. aeruginosa*, MDR isolates were more common among non-ICU inpatient isolates than among ICU patient isolates, except in 2000. Among ciprofloxacin-resistant isolates from 1998 to 2001 (n = 137), rates of susceptibility, intermediacy, and resistance to imipenem were 80.3, 0, and 19.7%, respectively, and those to meropenem were 83.9, 1.5, and 14.6%, respectively. Interpretative phenotype agreement for imipenem and meropenem against combined non-ICU inpatient and ICU patient isolates of *A. baumannii* (n = 421) from 1998 to 2001 was 91.2%. The most common discordant phenotypes observed were imipenem-resistant–meropenem-susceptible (4.0% of isolates) and imipenem-susceptible–meropenem-resistant (2.9% of isolates). Imipenem-resistant–meropenem-intermediate and imipenem-intermediate–meropenem-resistant isolates were not detected. Major error (i.e., susceptible to one carbapenem and resistant to the other) and minor error (i.e., intermediate to one carbapenem and susceptible or resistant to the other) rates were 6.9 and 1.9%, respectively, for 1998 to 2001.

DISCUSSION

The potential for antimicrobial resistance is an important concern for clinicians treating patients with confirmed or suspected *P. aeruginosa* or *A. baumannii* infections. In the present study, cumulative 1998 to 2001 results for *P. aeruginosa* demonstrated that >90% of the isolates tested were susceptible to amikacin and piperacillin-tazobactam; 80 to 90% of isolates were susceptible to cefepime, ceftazidime, imipenem, and meropenem; and 70 to 80% of isolates were susceptible to ciprofloxacin, gentamicin, levofloxacin, and ticarcillin-clavulanate (Table 1). Centralized in vitro studies conducted from 1997 to 2002 in the United States have published susceptibility results similar to those reported here for all agents except for piperacillin-tazobactam, for which slightly lower susceptibilities (78 to 90%) were reported previously (12, 15, 17, 25, 28).

Other studies conducted across consecutive years in the United States (1997 to 1999 and 1999-2000) have generally noted only marginal decreases in susceptibilities to aminoglycosides, β-lactams, and fluoroquinolones (12, 15, 17, 28). However, the percentage of fluoroquinolone-susceptible isolates identified in this study and other recent studies (approximately 70%) (12, 15, 17, 25, 28) is substantially lower than that reported in some studies conducted in 1997, in which susceptibilities were 85% for levofloxacin and 89% for ciprofloxacin (8, 26). Fluoroquinolone susceptibility among *P. aeruginosa* isolates appears to be decreasing in the United States, perhaps because of increasing or cumulative fluoroquinolone use, the lack of adherence to approved infection control practices by

hospitals, or changes to the public health infrastructure (15). Susceptibility to fluoroquinolones appears to be decreasing at a higher rate than is susceptibility to other antimicrobial classes. Perhaps cumulative fluoroquinolone use is a greater selector of resistance than is cumulative use of aminoglycosides, carbapenems, or other β-lactams, or maybe fluoroquinolone-resistant strains are more easily spread than are strains resistant to other agents.

Susceptibility to ceftazidime (3.6%), ticarcillin-clavulanate (4.4%), imipenem (6.4%), and meropenem (7.3%) was higher among isolates from non-ICU inpatients than among isolates from ICU patients (Table 1), as reported previously by the National Nosocomial Infections Surveillance system (23). Similar rates of susceptibility to amikacin, fluoroquinolones, and piperacillin-tazobactam among isolates from non-ICU inpatients and ICU patients may reflect heavier usage of these agents outside the ICU than of agents with higher relative susceptibility differences (i.e., ceftazidime, ticarcillin-clavulanate, imipenem, and meropenem); however, other factors such as adherence to infection control practices may also be influencing this trend. Fluoroquinolone resistance is a problem both inside and outside the ICU in hospitals. The possible loss of the fluoroquinolones to treat all *P. aeruginosa* infections implies that injectable therapy with alternative agents and possibly hospitalization may be required to treat these infections in the future (6, 12).

Cumulative 1998 to 2001 results for *A. baumannii* demonstrated that >90% of isolates tested were susceptible to imipenem (96.5 and 96.6%) and meropenem (91.6 and 91.7%) while far fewer isolates were susceptible to any other agent (i.e., 70 to 80% susceptibility to amikacin and ticarcillin-clavulanate) (Table 6). Centralized in vitro studies conducted from 1997 to 2000 in the United States have published similar susceptibility results for all agents tested in the present study with two notable exceptions (11, 17, 25, 28). Nosocomial isolates of *A. baumannii* (n = 150) collected from patients in the United States and Canada as part of the SENTRY surveillance program from 1997 to 1999 (11) demonstrated carbapenem susceptibilities 4 to 8% lower and ciprofloxacin and gentamicin susceptibilities 30% higher than those reported in the present study. The MYSTIC surveillance program, reporting on a limited number of *A. baumannii* isolates (32 in 1999 and 56 in 2000), found a 15%-lower rate of susceptibility to carbapenems, a 30%-higher rate of susceptibility to ciprofloxacin, and a 15- to 20%-higher rate of susceptibility to gentamicin than those in the present study (25). Carbapenems remain the agents of choice for infections with *Acinetobacter*, although outbreaks of imipenem-resistant *Acinetobacter* have been reported and carbapenem resistance among *A. baumannii* can be endemic in certain hospitals (1, 19, 21, 32). The surveillance data presented in this study and other recent studies (11, 17, 25, 28) demonstrate that levofloxacin and ciprofloxacin activities are limited against *A. baumannii*, with approximately 50% of isolates being resistant to fluoroquinolones. Fluoroquinolone susceptibilities are now considerably lower than the rates of 70 to 80% reported in studies conducted in 1997 (8, 14). *A. baumannii* susceptibility to piperacillin-tazobactam was previously reported to have decreased from 72 to 59% from 1999 to 2000 (25); a similar observation was made in the present study,

TABLE 3. Percentages of isolates resistant to other antimicrobials among isolates of *P. aeruginosa* from non-ICU inpatients[a] and ICU patients[b] stratified by their imipenem and meropenem susceptibility status in 2001

Patient type	Carbapenem phenotype[c]	No. of isolates	% of isolates resistant								
			Amikacin	Cefepime	Ceftazidime	Ciprofloxacin	Gentamicin	Imipenem	Levofloxacin	Meropenem	Piperacillin-tazobactam	Ticarcillin-clavulanate
Non-ICU inpatients	Imipenem susceptible	932	3.0	5.2	6.2	22.9	13.0	0	19.7	1.6	5.3	19.3
	Imipenem resistant	170	18.2	30.0	30.6	68.8	54.1	100	66.5	54.7	23.5	57.6
ICU patients	Imipenem susceptible	201	3.0	4.5	7.5	20.4	10.4	0	17.4	2.5	3.0	26.9
	Imipenem resistant	63	39.7	38.1	36.5	76.2	73.0	100	71.4	66.7	28.6	71.4
Non-ICU inpatients	Meropenem susceptible	975	3.4	5.1	6.7	24.2	12.9	4.6	21.2	0	5.0	17.3
	Meropenem resistant	120	22.5	36.7	35.8	75.0	67.5	77.5	72.5	100	28.3	85.0
ICU patients	Meropenem susceptible	214	3.7	5.1	7.9	22.0	12.6	7.0	18.2	0	2.8	25.2
	Meropenem resistant	50	50.0	42.0	36.0	84.0	84.0	84.0	82.0	100	40.0	92.0

[a] In 2001, 1,143 isolates from non-ICU inpatients were simultaneously tested with amikacin, cefepime, ceftazidime, ciprofloxacin, gentamicin, imipenem, levofloxacin, meropenem, piperacillin-tazobactam, and ticarcillin-clavulanate.

[b] In 2001, 272 isolates from ICU inpatients were simultaneously tested with amikacin, cefepime, ceftazidime, ciprofloxacin, gentamicin, imipenem, levofloxacin, meropenem, piperacillin-tazobactam, and ticarcillin-clavulanate.

[c] Imipenem-intermediate isolates from non-ICU inpatients (n = 41) and ICU patients (n = 8) and meropenem-intermediate isolates from non-ICU inpatients (n = 48) and ICU patients (n = 8) were infrequent (<50 isolates per group) and were excluded from analysis.

TABLE 4. Comparison of imipenem and meropenem MIC interpretative phenotypes for 5,614 isolates of *P. aeruginosa* (combined 1998 to 2001 data)[a]

Meropenem phenotype	% of isolates with imipenem phenotype/annum		
	Susceptible	Intermediate	Resistant
Susceptible	80.9	1.9	3.1
Intermediate	0.9	0.6	2.3
Resistant	1.2	0.7	8.4

[a] The percentage of isolates with identical imipenem and meropenem phenotypes, i.e., the sum of isolates that have imipenem-susceptible–meropenem-susceptible, imipenem-intermediate–meropenem-intermediate, and imipenem-resistant–meropenem-resistant phenotypes, was 89.8.

where piperacillin-tazobactam susceptibility decreased from 73.3% in 1998 to 56.7% in 2001 among ICU patients (Table 6).

Outbreaks of MDR *P. aeruginosa* and *A. baumannii* inside and outside ICUs are an increasingly reported problem in hospitals (2, 4, 19). MDR phenotypes are slowly increasing in prevalence among *P. aeruginosa* (1, 7, 10, 31) and *A. baumannii* (10). Unfortunately, ongoing regional or national surveillance studies do not routinely report rates of MDR in *P. aeruginosa*, and the definitions of MDR in published studies have not been uniform (7, 10, 12, 28). In one U.S. centralized in vitro study from 1999, 3.7% of *P. aeruginosa* isolates were MDR, where MDR was defined as isolates resistant to three or more of the drugs ceftazidime, gentamicin, imipenem, and levofloxacin (28). In that study, resistance to a fluoroquinolone was always associated with resistance to at least one other class of antimicrobial agent (28). In another study, conducted from 1997 to 1999, 3.3% of *P. aeruginosa* isolates were MDR, where MDR was defined as resistance to piperacillin, ceftazidime, imipenem, and gentamicin (12). In the present study among *P. aeruginosa* isolates, MDR, defined as concurrent resistance to any three of the drugs ceftazidime, ciprofloxacin, gentamicin, and imipenem, was higher (non-ICU inpatients, 5.5 to 7.0%; ICU patients, 7.0 to 9.1%) than that reported by previous studies (12, 28). Rates of MDR among *P. aeruginosa* organisms isolated from non-ICU inpatients and ICU patients showed a subtly increasing trend from 1998 to 2001 (non-ICU inpatients, 5.5, 6.4, 6.3, and 7.0%, respectively; ICU patients, 7.4, 7.0, 9.5, and 9.1%, respectively). Rates of MDR among *A. baumannii* were higher than those for *P. aeruginosa*, reaching 32.5 and 24.2% in 2001 among isolates from non-ICU inpatients and ICU patients, respectively. In the present study, resistance to ciprofloxacin was more commonly found in isolates of *P. aeruginosa* (Table 2) and *A. baumannii* concurrently resistant to other agents, suggesting that perhaps fluoroquinolones may be an important driver of MDR. Given that combination treatment is generally recommended for suspected *Pseudomonas* and *Acinetobacter* infections, there is a risk that this approach too may be encouraging resistance to multiple agents. Data suggest that currently the choice of a carbapenem, cefepime, or piperacillin-tazobactam in combination with amikacin or tobramycin would give the widest potential empirical activity against *P. aeruginosa* (15).

Carbapenems are resistant to hydrolysis by most β-lactamases and therefore are effective agents against a broad range of nosocomial pathogens (5). Subtle differences in the in vitro activities of imipenem and meropenem against *P. aeruginosa* and *A. baumannii* may exist as a result of differences in their resilience in response to known resistance mechanisms (20). However, resistance to both imipenem and meropenem appears to have been stable over time, and marginal differences

TABLE 5. Susceptibility of *P. aeruginosa* to antimicrobial agents according to patient age (combined 1998 to 2001 data)

Antimicrobial	Age (yrs)	Total no.	% Susceptible	% Intermediate	% Resistant
Amikacin	0–10	5,199	95.3	2.0	2.8
	11–20	2,671	76.4	5.7	17.9
	21–30	2,883	80.4	4.8	14.8
	31–60	15,330	91.5	3.8	4.7
	>60	25,090	94.8	2.8	2.4
Cefepime	0–10	3,786	90.2	6.2	3.6
	11–20	1,949	79.3	9.3	11.3
	21–30	2,049	77.5	9.6	13.0
	31–60	10,924	80.9	10.7	8.4
	>60	16,163	81.9	10.6	7.5
Ceftazidime	0–10	6,309	89.9	4.2	5.9
	11–20	3,105	85.2	4.8	10.0
	21–30	3,364	82.7	5.1	12.2
	31–60	19,000	84.7	6.3	9.0
	>60	33,876	86.2	5.8	8.0
Ciprofloxacin	0–10	5,809	96.3	1.0	2.7
	11–20	2,981	78.3	7.1	14.6
	21–30	3,330	66.4	6.9	26.7
	31–60	18,488	69.9	4.4	25.7
	>60	33,136	72.2	3.0	24.8
Gentamicin	0–10	6,847	86.9	5.9	7.2
	11–20	3,362	70.0	8.0	22.0
	21–30	3,691	68.5	8.5	22.9
	31–60	20,754	75.8	7.5	16.8
	>60	36,760	79.1	6.7	14.2
Imipenem	0–10	5,402	92.8	1.6	5.6
	11–20	2,615	86.4	2.1	11.5
	21–30	2,822	81.4	3.1	15.5
	31–60	15,569	83.0	2.7	14.3
	>60	27,319	85.5	2.6	12.0
Levofloxacin	0–10	3,169	96.1	1.4	2.6
	11–20	1,516	81.3	5.0	13.7
	21–30	1,981	67.3	5.5	27.2
	31–60	10,934	67.7	4.7	27.6
	>60	18,782	69.4	4.0	26.7
Meropenem	0–10	911	95.6	1.4	3.0
	11–20	524	79.2	5.2	15.6
	21–30	469	74.0	6.2	19.8
	31–60	2,013	81.7	4.5	13.8
	>60	2,903	86.6	3.5	9.9
Piperacillin-tazobactam	0–10	3,802	95.1	—[a]	4.9
	11–20	1,751	92.9	—	7.1
	21–30	2,010	88.2	—	11.8
	31–60	11,483	91.0	—	9.0
	>60	19,609	92.1	—	7.9
Ticarcillin-clavulanate	0–10	1,882	86.3	—	13.7
	11–20	1,041	77.0	—	23.0
	21–30	1,438	72.7	—	27.3
	31–60	7,744	75.0	—	25.0
	>60	13,470	78.1	—	21.9

[a] —, NCCLS breakpoint unavailable.

TABLE 6. Per-annum and combined 1998 to 2001 in vitro susceptibilities to 10 antimicrobial agents for clinical isolates of *A. baumannii* from non-ICU inpatients and ICU patients in the United States

Antimicrobial	Yr	Total no.		% Susceptible		% Intermediate		% Resistant	
		Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU	Non-ICU	ICU
Amikacin	1998	1,275	273	77.2	82.8	4.2	6.2	18.7	11.0
	1999	810	233	82.2	76.8	5.8	8.6	12.0	14.6
	2000	777	252	81.2	80.2	5.9	7.9	12.9	11.9
	2001	836	386	75.8	84.5	6.8	6.5	17.3	9.1
	1998–2001	3,698	1,144	78.8	81.6	5.5	7.2	15.7	11.3
Cefepime	1998	497	134	56.3	45.5	19.7	24.6	23.9	29.9
	1999	475	141	54.3	48.9	18.5	10.6	27.2	40.4
	2000	646	190	50.0	55.3	19.4	14.2	30.7	30.5
	2001	820	385	47.2	56.4	22.6	21.3	30.2	22.3
	1998–2001	2,438	850	51.2	53.2	20.3	18.5	28.5	28.4
Ceftazidime	1998	1,463	389	50.1	65.3	22.1	20.6	27.8	14.1
	1999	1,007	365	50.3	54.8	26.6	26.6	23.0	18.6
	2000	1,019	405	47.9	52.6	26.0	20.2	26.1	27.2
	2001	1,025	489	45.2	49.3	23.0	25.4	31.8	25.4
	1998–2001	4,514	1,648	48.5	55.1	24.2	23.2	27.3	21.7
Ciprofloxacin	1998	1,571	407	41.4	52.8	1.3	2.0	57.3	46.2
	1999	1,027	330	42.8	53.6	2.0	1.5	55.1	44.8
	2000	1,019	365	43.1	45.8	0.7	3.0	56.2	51.2
	2001	825	405	35.4	44.9	1.6	1.2	63.0	53.8
	1998–2001	4,442	1,507	41.0	49.2	1.4	1.9	57.6	48.9
Gentamicin	1998	1,714	452	43.6	58.2	2.2	2.2	54.3	39.6
	1999	1,238	428	47.8	49.3	2.3	2.3	49.8	48.4
	2000	1,202	449	48.0	51.4	2.1	2.2	49.9	46.3
	2001	1,167	546	44.3	52.9	2.9	3.3	52.8	43.8
	1998–2001	5,321	1,875	45.7	53.0	2.3	2.6	51.9	44.4
Imipenem	1998	1,376	352	98.0	96.6	0.4	0.6	1.6	2.8
	1999	1,005	315	97.4	94.9	0.4	1.0	2.2	4.1
	2000	963	340	96.3	98.5	0.2	0.3	3.5	1.2
	2001	912	373	93.4	96.2	0.4	0.0	6.1	3.8
	1998–2001	4,256	1,380	96.5	96.6	0.4	0.4	3.1	3.0
Levofloxacin	1998	455	—[a]	47.9	—	1.3	—	50.8	—
	1999	589	95	51.6	54.7	1.5	2.1	46.9	43.2
	2000	871	189	47.4	56.6	3.7	5.3	48.9	38.1
	2001	776	323	44.7	53.9	4.0	2.2	51.3	44.0
	1998–2001	2,691	626	47.6	55.1	2.9	3.0	49.5	41.9
Meropenem	1998	71	—	97.2	—	1.4	—	1.4	—
	1999	57	—	94.7	—	1.8	—	3.5	—
	2000	190	—	93.2	—	0.5	—	6.3	—
	2001	134	57	85.1	91.2	4.5	0	10.4	8.8
	1998–2001	452	96	91.6	91.7	2.0	0	6.4	8.3
Piperacillin-tazobactam	1998	539	165	65.1	—	21.2	—	13.7	—
	1999	491	188	65.2	—	14.3	—	20.6	—
	2000	731	210	57.7	—	19.4	—	22.9	—
	2001	641	358	58.4	—	18.4	—	23.2	—
	1998–2001	2,402	921	61.1	—	18.5	—	20.4	—
Ticarcillin-clavulanate	1998	1,051	323	71.4	—	3.0	—	25.6	—
	1999	605	230	71.4	—	8.6	—	20.0	—
	2000	418	234	71.8	—	5.7	—	22.5	—
	2001	300	195	69.3	—	8.7	—	22.0	—
	1998–2001	2,374	982	71.2	—	5.6	—	23.2	—

[a] —, <50 isolate results available.

in their activities have remained constant (Tables 3 and 4) (8, 11, 12, 15–17, 24–26, 28). Cross-resistance between imipenem and meropenem exceeded 60% in *P. aeruginosa*, and concordance in susceptibility classification was approximately 90%. *A. baumannii* is now frequently resistant to penicillins and cephalosporins including cefepime but rarely to carbapenems (3). Rigorous monitoring for MDR among *Pseudomonas* and *Acinetobacter* isolates is very important because outbreaks of

strains resistant to potentially useful agents, including carbapenems, have been reported elsewhere (19). In hospitals in Brooklyn, New York, the increase in MDR *A. baumannii* correlated with cephalosporin usage (19).

In conclusion, antimicrobial resistance rates among *P. aeruginosa* and *A. baumannii* are increasing slowly for most agents. However, fluoroquinolone resistance appears to be increasing more rapidly than is resistance to other agents and is the most common resistance component found among MDR isolates. The lack of any new compounds in the near future indicates that national, regional, and local surveillance efforts are imperative to provide clinicians with information for choosing empirical or directed therapy.

ACKNOWLEDGMENTS

We thank each of the participating institutions in TSN Database-USA for permitting surveillance data collection.

The publication of these data was supported financially by Merck Research Laboratories (West Point, Pa.).

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